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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/847,392	05/03/2001	Vitaly Arkadievich Livshits	206440US0CONT	8292

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 04/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/847,392	LIVSHITS ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *8-12* is/are allowed.

6)☒ Claim(s) *13-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/396,357.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

The request filed on 9-17-03 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 09/847,392 is acceptable and a RCE has been established. An action on the RCE follows.

Claims 8-28 are now at issue and are present for examination.

Applicants' amendments and arguments filed on 9-17-03, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

The disclosure is objected to because of the following informalities: Applicants to not provide the relationship of the instant application to the parent application on the first line of the specification. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-16, 21-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 and 21 recite the phrase "wherein said DNA is hybridized under stringent conditions...". It is not clear to the Examiner as to whether the

hybridization is done before amplifying the copy number in the cell or after. It appears that applicant's amendment of the claim in response to the previous objection has rendered the claim more confusing. In the previous Office action claim 13 was objected for a grammatical error. Claim 13 previously recited the phrase "wherein said DNA is hybridizes" which was grammatically improper. Such an objection would have been overcome simply by deleting the word "is". Now again Examiner suggests that applicants need to amend the claim to recite the phrase as follows, " wherein said DNA hybridizes under stringent conditions" in order to overcome the current rejection.

Claims 13-16, 21-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13 and 21 recite the phrase the phrase "under stringent conditions". A perusal of the specification provides a definition which is very vague or incomplete or at best exemplary. In order to take advantage of the exemplary definition provided in the specification for support and to clearly define the phrase "stringent conditions", Examiner suggests amending the claim as follows, "wherein said DNA sequence hybridizes to nucleotides 557 to 1171 of SEQ ID NO:1, under hybridization conditions in which polynucleotides that are at least 70% identical to nucleotides 557 to 1171 of SEQ ID NO:1 would hybridize to nucleotides 557 to 1171 of SEQ ID NO:1, and wherein said DNA encodes....".

In response to the previous Office action, applicants indicate that they have amended the claim taking the suggestions of the Examiner. However, applicants have not established the link between the hybridization conditions exactly as suggested by the Examiner, but kept the

stringent hybridization conditions and the per cent homology language separate. Therefore the above rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making amino acids using a bacterium expressing DNA with SEQ ID NO:1 or nucleotides 557 to 1171 of SEQ ID NO:1, encoding polypeptide with amino acid sequence of SEQ ID NO:2 wherein said polypeptide renders the cells in which the DNA is expressed, homoserine resistant, does not reasonably provide enablement for such a method in which a bacterium expressing any DNA which hybridizes under stringent conditions to nucleotides 557-1171 of SEQ IDNO:1 and is at least 70% homologous to nucleotides 557 to 1171 of SEQ ID NO:1 and encodes a protein having an activity of rendering a bacterium homoserine resistant including any variant, mutant or recombinant, is used. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 13-28 are so broad as to encompass a method for making amino acids using a bacterium expressing any DNA which is a variant, mutant or a recombinant of nucleotides 557-1171 of SEQ ID NO:1 with at least 70% identity thereto and also capable of hybridizing under stringent conditions (specific conditions not being clear) to SEQ ID NO:1 encoding a protein which renders a bacterium homoserine resistant including any variant, mutant or recombinant of said DNA. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of DNA sequences that are broadly encompassed by the method claims.

Applicants propose to use the bacteria transformed with above polynucleotides for recombinant process of production of amino acids. Since the nucleotide sequence determines the type of protein and the ultimate function of the encoded protein and since the predictability of which changes in the nucleotide sequence can be tolerated and still obtain a protein having the desired activity, requires a knowledge of and guidance with regard to which amino acids can be altered and which cannot be altered and a detailed knowledge of the ways in which the encoded protein structure relates to its function, changing the nucleotide sequences as proposed by the applicants and/or addition of substantial amount of additional nucleotide sequence unrelated to the nucleic acid sequence of SEQ ID NO:1 may not lead to desired function of the polynucleotides in said bacterium. This is because the changes suggested by the applicants will result in an enormous number of nucleotide sequences that may or may not encode the polypeptide which renders the cells resistant to homoserine. It would require undue

experimentation by the skilled artisan to make and use the polynucleotides as claimed in the claims. The specification is limited to teaching the use of SEQ ID NO: 1 and nucleotides 557 to 1171 of SEQ ID NO:1 for encoding a protein that renders a bacterium homoserine resistant which property is made use of the in the above method claims, but provides no guidance with regard to the making of variant and mutant polynucleotides that are 70% identical in sequence to SEQ ID NO:1 and its use in the above method or with regard to other uses of such polynucleotides. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides for use in the above method, the lack of guidance, working examples, and unpredictability of the art in predicting function from an encoded polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or modifications of nucleotides, as encompassed by the instant claims, and the base changes within a nucleic acid's sequence can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given DNA to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any DNA which is a variant/mutant or having 70% homology to nucleotides 557-1171 of SEQ ID NO:1 and encoding a protein which imparts homoserine resistance to a bacterium because the specification does not establish: (A) regions of the DNA sequence which may be modified without effecting the above mentioned activity/utility; (B) the general tolerance of homoserine resistance imparting DNA sequence to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide sequence with an expectation of obtaining the desired biological function and utility; (D)a specific hybridization condition and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of making amino acids using bacteria expressing any or all DNA which are at least 70% homologous to and hybridizes to SEQ ID NO:1 or nucleotides 557-1171 of SEQ ID NO:1 under "stringent conditions" and encoding a protein which imparts homoserine resistance to said bacterium. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of DNAs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action applicants have amended claims 8-11 to overcome the above rejection and added new claims. However, rejections have been applied to new claims as well. Applicants submit that with respect to claim 13, provided with nucleotide sequence in SEQ ID NO:1 and the tools necessary to hybridize one DNA to another DNA and determine whether it has necessary homology and activity, is within the well-described knowledge available in the art and in support of that applicants submit specific pages taken from a laboratory manual. Applicants also argue that homology searches can be done using the BLAST and FASTA search engines.

In response to the issues raised by the Examiner Applicants compare the RhtB protein with lysE gene and argue that those skilled in the art know that as in LysE gene, even in the RhtB gene the transmembrane domains are highly conserved and would be able to perform PCR reactions to obtain such highly conserved domains and therefore would not require undue experimentation. Applicants argue that PCR is a well known method that is routinely followed by those skilled in the art. Examiner agrees with the applicants that PCR is a highly common technique practiced in the art. However, Examiner respectfully disagrees with the applicants' argument that using such PCR technique to amplify conserved domains, it would be possible for those skilled in the art to obtain a variant as claimed by the applicants for practicing the method. While applicants provide argument that it would be well within the skill of those practicing the art to make conserved transmembrane domains (and Examiner has not argument against it) by PCR, they are silent regarding the guidance to vary sequences that are not conserved or do not constitute the transmembrane domains.

Next, applicants argue that at page 6 of the specification a detailed explanation of how the artisan may clone and vary sequences are provided. Examiner respectfully disagrees. While some general explanations are provided detailed explanation as to which specific amino acid residues can be changed while retaining the functional properties of the polypeptide are not provided. Determination of the activity of the polypeptide is not what the Examiner is questioning. It is agreed that applicants provide the assay to test the polypeptide. However, the specification fails to provide guidance to make the variant polynucleotides to encode variant polypeptides that applicants propose to use in the method.

Applicants also allege that Examiner is confusing the quantity of experimentation with undue experimentation. Examiner assures the applicants, that such a confusion does not exist in the Examiner's mind and the rejection is not based on any such confusion. As argued in his previous arguments, Examiner reiterates while methods to make changes in a polynucleotide or polypeptide are well known to the skilled artisan, producing and using polynucleotides as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance as to where or which specific amino acid sequence(s) need to be changed while retaining the function of the polypeptide. Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing all of the virtually infinite permutations and combinations of the amino acids in the sequence. This would clearly constitute undue experimentation. It is clear to the Examiner that while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has not been provided in the instant

specification. As stated above the specification does not establish: (A) regions or specific nucleotide bases of the DNA sequence which may be modified without effecting the above mentioned activity/utility; (B) the general tolerance of homoserine resistance imparting DNA sequence to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide sequence with an expectation of obtaining the desired biological function and utility; (D) specific high-stringency hybridization conditions and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Therefore the above rejection is maintained for claims 13-28.

Examiner has withdrawn the previous rejection of claims 17-20 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in view of amendment to claim 17.

Terminal Disclaimer

The terminal disclaimer filed on 3-4-03 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent No. 6,303,348 has been reviewed and is accepted. The terminal disclaimer has been recorded.

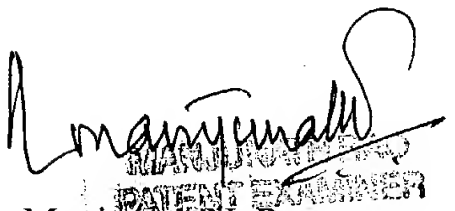
Provisional rejection of claims 8-11 under the judicially created doctrine of obviousness-type double patenting as being non-patentable over claims 1-4 of US Patent No. 6,303,348 is withdrawn.

Allowable Subject Matter

Claims 8-12 are allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao
April 26, 2004